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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GABEL, GAILENE	
ART UNIT	PAPER NUMBER
1641	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/14/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/635,972	WILLMANN ET AL.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's amendment and response, filed on December 4, 2006, is acknowledged and has been entered. Claims 17 and 30 have been amended. Currently, claims 17-32 are pending. Claims 17-32 are under examination.

Claim Status

2. It is noted that claims 19-29, 31, and 32 are designated with incorrect claim status in this Applicant's amendment filed on December 4, 2006. Claims 19-29, 31, and 32 are not "new" claims since they have been submitted as new claims in the previous Applicant's amendment filed on July 5, 2006. Therefore, for this instant amendment, claims 19-29, 31, and 32 should be designated as "previously presented" claims. Applicant is advised to comply with the Revised Amendment Practice (37 CFR 1.121) in reply to this Office Action.

Withdrawn Objections/Rejections

3. All rejections not reiterated herein, have been withdrawn.

4. In light of Applicant's argument, the rejection of claims 17-32 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 5-18 of U.S. Patent No. 6,495,333, is hereby, withdrawn.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 17-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17, step c), as amended, lacks antecedent basis in reciting, "wherein the binding of the dendritic cell-distinguishing antibodies" because step b) only provides "adding to the sample a plurality of dendritic cell-distinguishing antibodies" and step c) only provides "flow cytometrically assaying ... for the binding of said antibody specific for said dendritic cell surface activation marker." Accordingly, there is no antecedent basis for the recitation of "the binding of the dendritic cell-distinguishing antibodies" in step c), nor is there an indication thereafter of what structural elements it specifically binds.

Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 17-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a flow cytometric method for measuring dendritic cell function in whole blood comprising:

a) contacting the whole blood sample with a dendritic cell activator,

b) adding to the sample a plurality of dendritic cell- distinguishing antibodies that bind to non-dendritic cells, at least one dendritic cell-subsetting antibody that binds to dendritic cell surface structure, and at least one antibody specific for a dendritic cell surface marker indicative of activation;

c) lysing the erythrocytes in the resulting sample; and then

d) flow cytometrically assaying the sample for binding of the antibodies recited in step b) with cell antigens specific thereto;

does not reasonably provide enablement for a method in which 1) the lysing step is omitted, nor is it enabled for 2) a positive identification of dendritic cells in a whole blood sample by using only dendritic cell-distinguishing antibodies and at least one antibody specific for dendritic cell surface marker indicative of activation, absent further specific use of at least one dendritic-cell subsetting antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

As set forth in In re Wands, 858 F .2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), enablement requires that the specification teach those in the art to make and use the

invention without undue experimentation. Factors to be considered in determining, whether a disclosure would require undue experimentation include 1) the nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of those in the art, and 8) the breadth of the claims.

The nature of the invention- the invention is directed to a flow cytometric method for measuring dendritic cell function by contacting the whole blood sample with a dendritic cell (DC) activator; adding to the sample a plurality of labeled DC-distinguishing antibodies, at least one labeled DC subsetting antibody, and at least one labeled DC surface marker antibody indicative of activation; lysing the erythrocytes in the sample; then flow cytometrically assaying the sample for binding of the DC-distinguishing antibodies to DC, binding of the DC-subsetting antibody to a subset of the DC, and binding of the DC cell surface marker antibody indicative of activation to its specific cell surface marker, the latter binding of which provides indication of dendritic cell function.

The state of the prior art- the prior art of record fails to disclose a method for flow cytometrically measuring dendritic cell function wherein specific targeting and identification of specific DC subsets using antibodies specific thereto and lysis of erythrocytes, are omitted from the assay.

The predictability or lack thereof in the art- there is no predictability based on the instant specification that the claimed method will work absent use of antibodies specific for targeting and identifying specific DC subsets and lysis of erythrocytes in the assay.

The amount of direction or guidance present- appropriate guidance is provided by the specification for the claimed method to work using subsetting antibodies for targeting and identifying specific DC subsets and lysis solution for lysing erythrocytes in the assay. However, the specification fails to provide any guidance to enable the claimed method to work with exclusion of the two aforementioned elements.

The presence or absence of working examples- working examples are provided in the specification that a show using subsetting antibodies for targeting and identifying specific DC subsets and lysis solution for lysing erythrocytes in the assay. There are no working examples that show analogous results when excluding the two aforementioned elements, which are encompassed by the broad scope of the instant claims.

The quantity of experimentation necessary- it would require undue amount of experimentation for the skilled artisan to make and use the method as claimed, in the absence of subsetting antibodies for targeting and identifying specific DC subsets and lysis solution for lysing erythrocytes in the assay, which are shown to be required to work in Applicant's disclosure.

The relative skill of those in the art-the level of skill in the art is high.

The breadth of the claims- as recited, the instant claims are directed to a flow cytometric method for measuring dendritic cell function by contacting the whole blood

sample with a dendritic cell (DC) activator; adding to the sample a plurality of DC-distinguishing antibodies and DC surface marker antibodies indicative of activation; then flow cytometrically assaying the sample for binding of the DC-distinguishing antibodies to DC, and binding of the DC cell surface marker antibody indicative of activation to its specific cell surface markers, the latter binding of which is claimed to provide an indication of dendritic cell function, without specifically showing how it can be done without undue experimentation.

The specification at pages 13-15 specifically states that dendritic cell-distinguishing antibodies must include 2 categories of antibodies that preferentially bind to non-dendritic cell lineage antibodies and subsetting antibodies that bind to dendritic cell surface structures useful in identifying dendritic cells, e.g. CD11 and CD123. The specification states that, to date, no cell surface marker alone positively identifies dendritic cells (specification at page 13, lines 29-32). The specification also requires that use of antibodies that bind to dendritic cell surface structures obligates the additional use of non-dendritic cell binding antibodies (page 14, lines 1-7). The non-dendritic cell binding antibodies exemplified in the specification include a mixture of antibodies specific for CD3, CD14, CD16, CD19, CD20, and CD56, each conjugated with fluorescein isothiocyanate (FITC) (page 13, lines 11-19). By using such antibody composition, the dendritic cells in the sample assort into the $FITC^-$ class or $FITC^{low}$ class. These $FITC^-/FITC^{low}$ classes are then labeled with "subsetting" antibodies that bind to CD11 or CD123. A typical surface staining scheme includes, e.g. $lin1^{FITC}$, $HLA\text{-}DR^{PerCP}$, CD11c APC. Thereafter, the dendritic cell surface markers specific for

dendritic cell activation are stained using fluorophore-conjugated antibodies that are specific for dendritic cell function. After surface staining, the red cells are lysed. Following lysis, the cells are then analyzed using flow cytometer (pages 16 and 17). Nowhere in the specification does it teach a method such as disclosed in claims 17-29.

The claims are further not enabled because various labels are disclosed in the specification as necessary, yet are not included in the claims.

Accordingly, one of ordinary skill in the art could not make and use the invention as claimed without undue experimentation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 17-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Olweus et al. (Peripheral Blood Dendritic Cells Revealed by Flow Cytometry, Becton Dickinson - Application Note 3, (1998)) in view of Becton Dickinson (Detection of Intracellular Cytokines in Activated Lymphocytes, Application Note 1, (1996)).

Olweus et al. teach a flow cytometric method for dendritic cell (DC) function in whole blood. Olweus et al. specifically provide that difficulty in studying DC for function in the whole blood stems from their low frequency in occurrence and lack of specific DC markers (see page 1-2). In practice, Olweus et al. teach adding to the whole blood sample CD-distinguishing antibodies (non-DC lineage cocktail of markers) collectively including antibodies to each one of CD3, CD14, CD16, CD19, CD20 and CD56 conjugated with fluorescent isothiocyanate (FITC). Olweus et al. teach further adding at least one DC-subsetting antibody selected from antibody to CD123 (IL-3Rα) and antibody to CD11c, both of which are specific markers that identify distinct DC subsets in the peripheral blood. Both CD123 and CD11c expressing cells also express high levels of HLA-DR. Hence, for cell surface marker labeling and differentiation, both anti-CD123 antibody and anti-CD11c antibody can be conjugated to phycoerythrin and anti-HLA-DR antibody may also be conjugated with PerCP (see page 4). Olweus et al. teach that CD83 and CMRF-44 are also cell surface markers that are expressed at high levels in cell surfaces of activated cultured dendritic cells in blood; therefore, antibody to each one of CD83 and CMRF-44 can be used in identifying dendritic cell activation (see

page 1). After the different populations and subsets of dendritic cells are labeled, erythrocytes are lysed using a FACS lysing solution (see page 5). Specifically, Olweus et al. disclose that known procedures have utilized selective growth of DCs in certain cytokine combinations.

Olweus et al. differ from the claimed invention in failing to teach contacting the whole blood sample with a dendritic cell activator to activate the dendritic cells. Olweus et al. also does not teach including antibody specific for CD4, as part of the DC-distinguishing antibodies.

Becton Dickinson teaches activating lymphocytic antigen presenting cells (dendritic cells) using lipopolysaccharide (LPS), phorbol 12-myristate 13 acetate and Ionomycin (PMA+I) and then testing the cells for cell surface staining using antibodies specific for cell surface antigens that are conjugated to a specific label (see page 4, column 1, page 5, column 1, and page 6, column 2). Becton Dickinson teaches that CD3, CD4, and CD8 are commonly used for T-lymphocyte subsetting and are generally modulated by PMA activation (see page 8, column 1). Although Becton Dickinson is silent in using CD40 cross-linker for modulating or stimulating or activating DC, CD40 cross-linker constitutes an obvious variation of dendritic cell activators that are well known and conventional in the art

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to activate the DC in the method of Olweus, using LPS or PMA+1 as taught by Becton Dickinson because Becton Dickinson specifically taught activating specific lymphocytic cells in order to obtain a measure of the level of DC activity in

blood, and Olweus specifically suggested the importance of obtaining accurate measure of these rare DC lineages present in blood and their corresponding function in order to elucidate the role of DC immune regulation in physiological and pathological conditions.

8. No claims are allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (571) 272-0820. The examiner can normally be reached on Monday, Tuesday, and Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Gailene R. Gabel
Patent Examiner
Art Unit 1641
February 2, 2007